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TITLE: Pupillometry and Saccades as Objective mTBI Biomarkers

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13. SUPPLEMENTARY NOTES
mild traumatic brain injury (mTBI), infrared pupillometers, King-Devick (KD) test, near point of convergence (NPC) rule, objective biomarkers

14. ABSTRACT

The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mild traumatic brain injury (mTBI) using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred mTBI and 100 age-matched non-TBI (controls) military personnel are to be recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed to determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Department of Brain Injury Medicine. Preliminary results showed that three of the eight PLR parameters are statistically different between the groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. In addition, the KD test, NPC rule, and the CISS survey showed sensitivity in identifying military personnel with mTBI.

15. SUBJECT TERMS

Nothing listed

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INTRODUCTION:
The DOD reported that 333,169 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.4% (DVBIC 2015). The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters (Marion 2011). The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mTBI using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred acute mTBI (≤72 hrs post injury) and 100 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed to determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Department of Brain Injury Medicine. There are five hypotheses being tested. First, those who have suffered acute mTBI/concussion will have abnormal PLR findings in comparison to controls. Second, those who have suffered acute mTBI/concussion will have abnormal KD test score in comparison to controls. Third, those who have suffered acute mTBI/concussion will have receded NPC compared to controls. Fourth, those who have suffered acute mTBI/concussion will have higher Convergence Insufficiency Symptoms Survey (CISS) scores in comparison to controls. Fifth, the PLR values measured by the PLR-200 pupillometer (research grade) are not different to those measured by the NPi-100 pupillometer (clinic grade).

BODY:
Major Task 1: Administrative Requirements
Subtask 1: Hire Optometrist and Ophthalmic Assistance: COMPLETED

Subtask 2: Purchase equipment and supplies: COMPLETED

Subtask 3: WAMC IRB approval: COMPLETED

Subtask 4: USAMRMC HRPO approval: COMPLETED

Major Task 2: Data Collection on Military Personnel at WAMC
Subtask 1: Procedures and data collection training/standardization: COMPLETED

Subtask 2: Complete data collection in 100 subjects with mTBI: COMPLETED

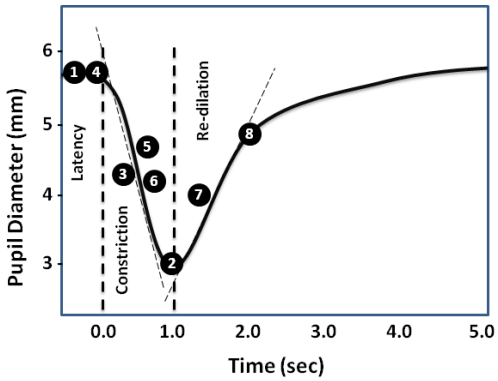
Subtask 3: Complete data collection in 100 age-matched control subjects (non-TBI): COMPLETED

Major Task 3: Data Analysis and Report Writing
Subtask 1: Complete progress report: COMPLETED

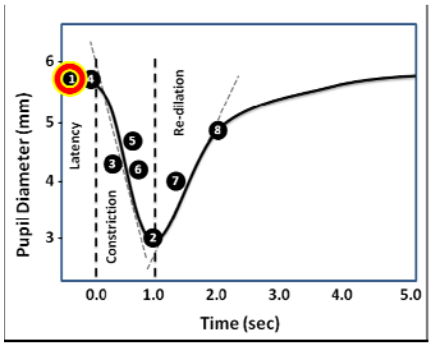
WAMC IRB and USAMRMC HRPO approved the study protocol continuing review on 14 March 2016. Quarterly reports (n = 3) were submitted during Year 2 to Contract Specialist, U.S. Army Medical Research Acquisition Activity and Science Officer, Congressionally Directed Medical Research Programs, USAMRMC, following the timeline indicated in the contract.

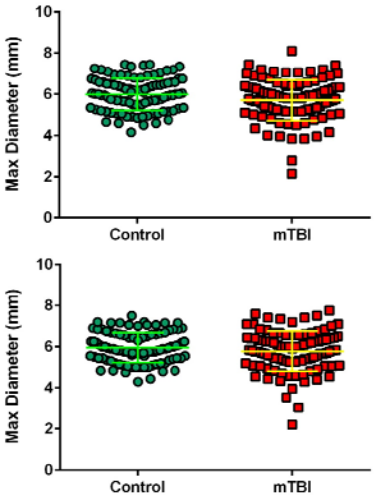
Subtask 2: Complete data analysis: PRELIMINARY ANALYSIS COMPLETED
All subjects were corrected to 20/20 and had similar spherical equivalent refractive error (mTBI -0.49 ± 2.07 D; non-TBI +0.12 ± 0.98 D; $p = 0.25$). All subjects, in both groups, had normal pupil response and no afferent pupil defect with the manual penlight examination. Pupillary light reflexes (Figure 1) and oculomotor functions can be affected by age; therefore, an accurate data analysis requires to age-match the experimental (mTBI) and the control subjects. Preliminary analysis was completed to evaluate initial results. The initial results compared monocular (right eye (OD; left eye (OS)) PLR of 100 Service members with mTBI during the acute stage (≤72 hrs) post injury and 100 age-matched controls who had neither experienced an mTBI nor been exposed to a blast event. The initial analysis showed that following results:

Figure 1. Schematic diagram of the pupillary reaction curve illustrating PLR recorded parameters: 1) maximum diameter; 2) minimum diameter; 3) percent of constriction; 4) constriction latency; 5) average constriction velocity; 6) maximum constriction velocity; 7) average dilation velocity; 8) 75% recovery time.

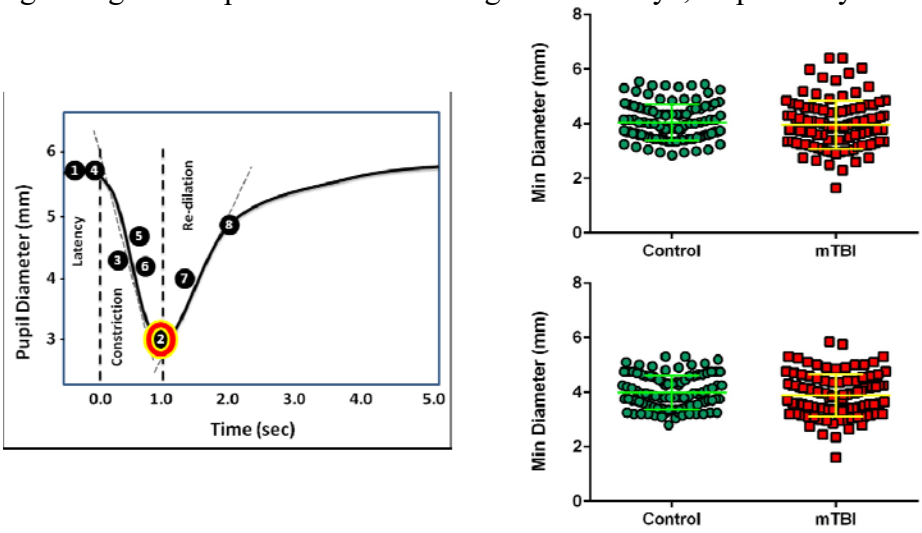


1) Maximum pupil diameter showed no significant difference between the acute mTBI and control group (OD $P = 0.201$; OS eye $P = 0.171$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

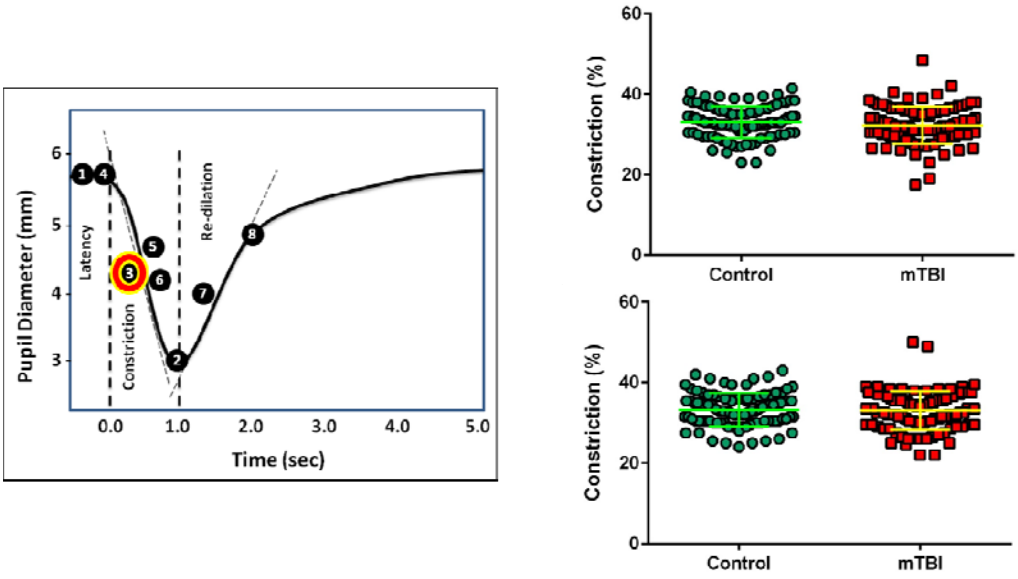




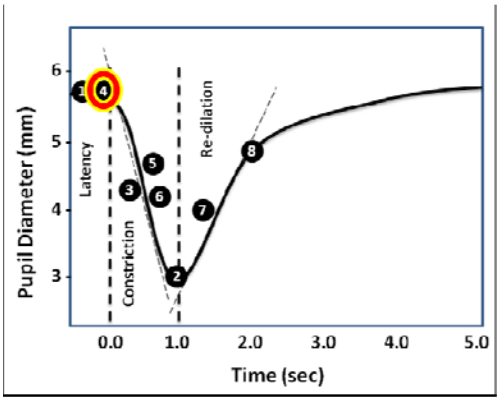
2) Minimal pupil diameter showed no significant difference between the acute mTBI and control group (OD $P = 0.431$; OS $P = 0.30$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

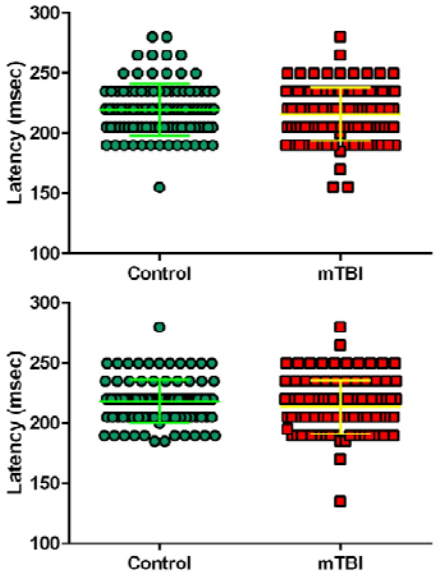


3) Percent of pupil constriction showed no significant difference between the acute mTBI and control group (OD $P = 0.188$; OS $P = 0.719$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

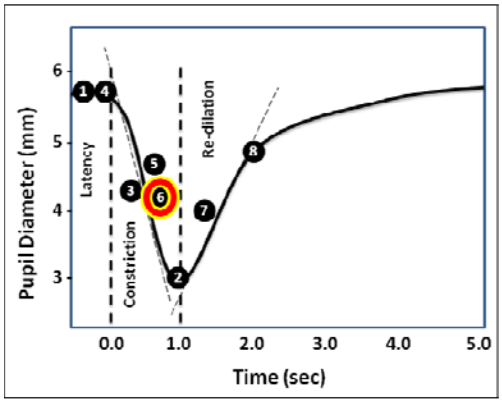


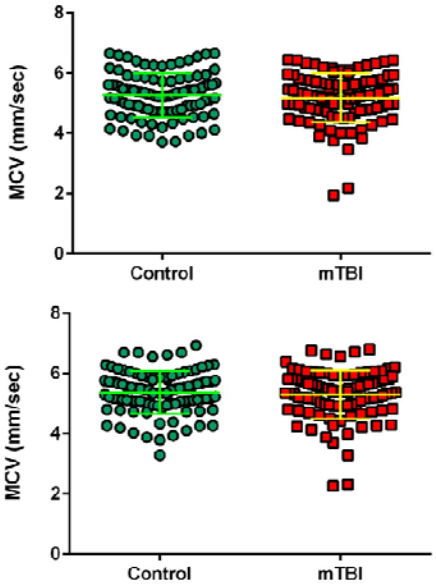
4) Constriction Latency (Con Lat) for the preliminary findings did not show a statistical difference (OD $P = 0.259$; OS $P = 0.108$), see figure below. This is inconsistent with the only pupillometry study in the literature in subacute patients (Capo-Aponte 2013); however time post-injury is different in both studies (acute vs. subacute). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.



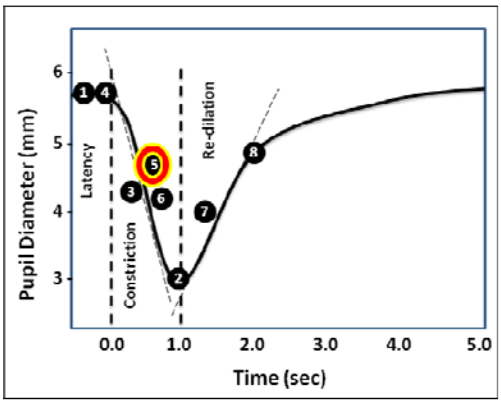


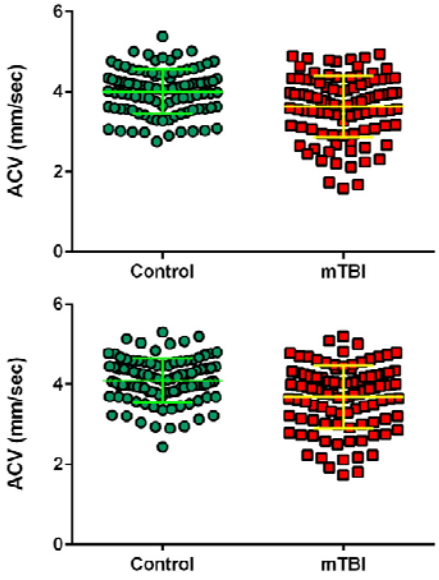
5) Maximum constriction velocity (MCV) for the preliminary findings did not have between groups statistical difference (OD $P = 0.423$; OS $P = 0.509$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.



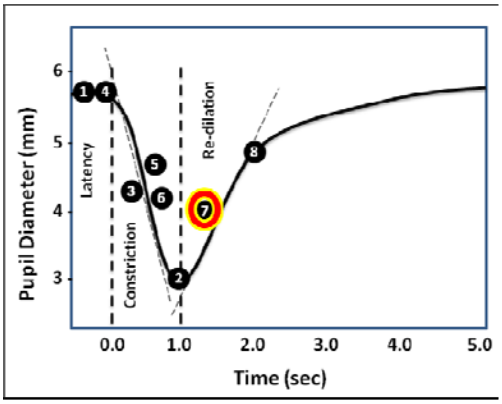


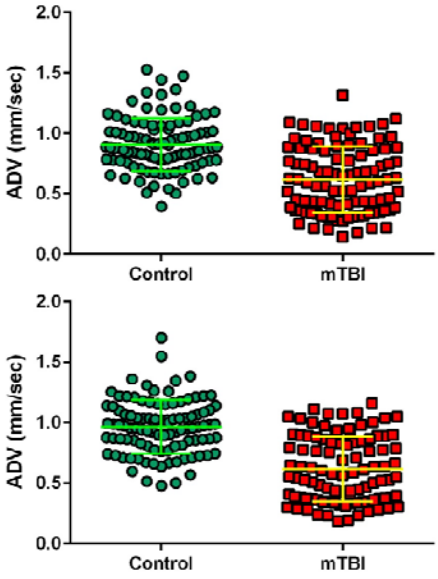
6) Average Constriction velocity is significantly reduced in mTBI subjects mTBI (OD *P* <0.0001; OS *P* = 0.0001), see figure below. This is in agreement with a previous study (Capo-Aponte 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.



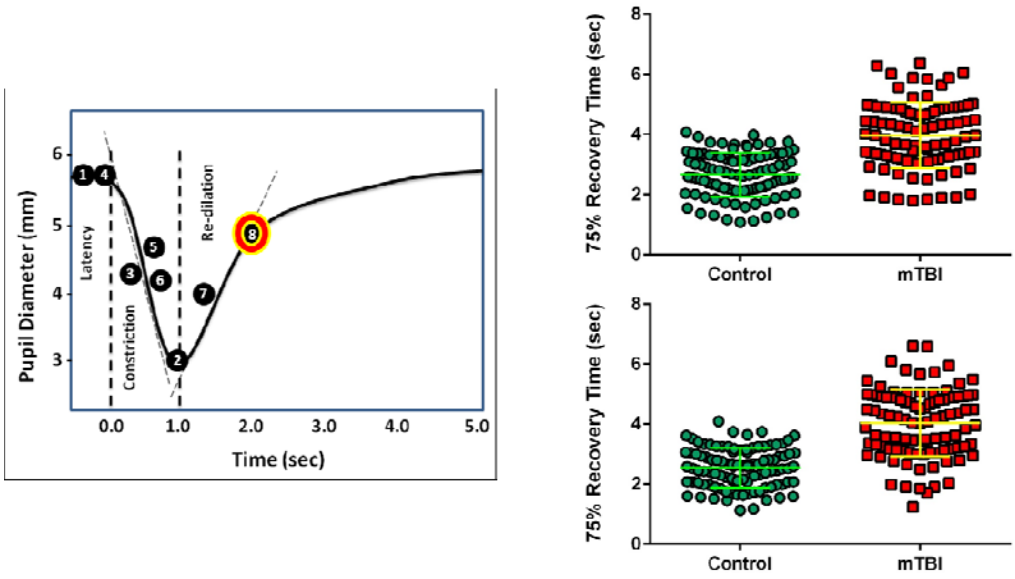


7) Average dilation velocity (ADV) is significantly reduced in mTBI subjects mTBI (OD *P* <0.0001; OS *P* <0.0001), see figure below. This is in agreement with a previous study (Capo-Aponte 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.

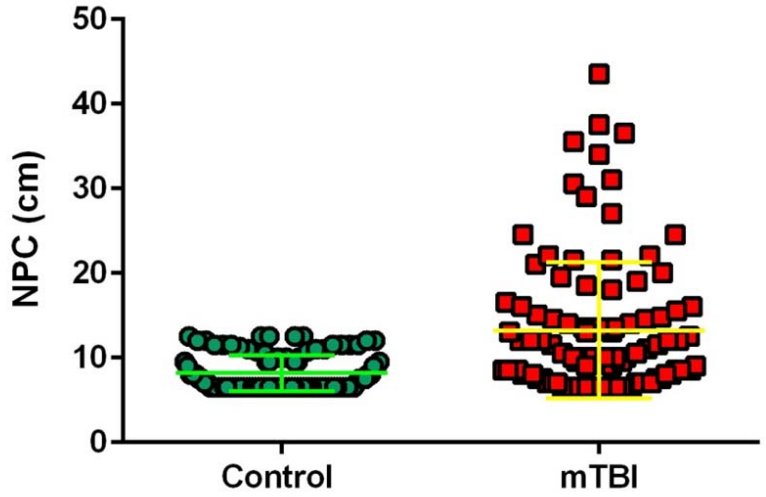




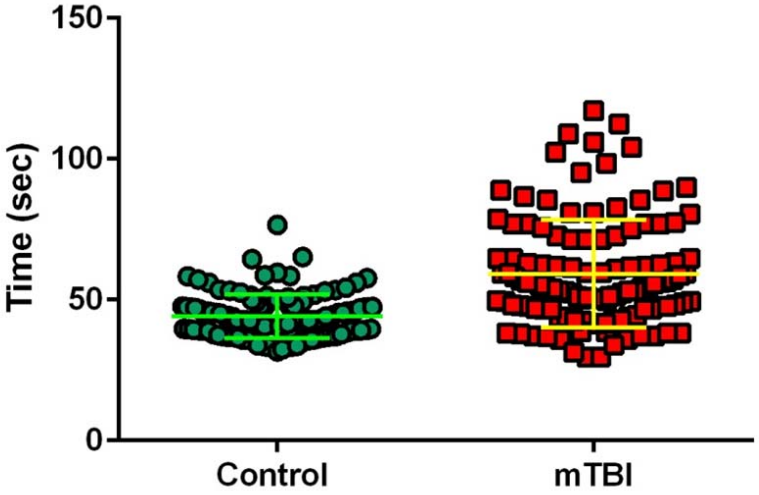
8) The total time taken by the pupil to recover 75% of the initial resting pupil size after it reached the peak of constriction is significantly longer in mTBI group (OD P <0.0001; OS P <0.0001), see figure below. This is in agreement with a previous study (Capo-Aponte 2013). Left PLR diagram; Top and Bottom Right diagrams depict the results for right and left eye, respectively.



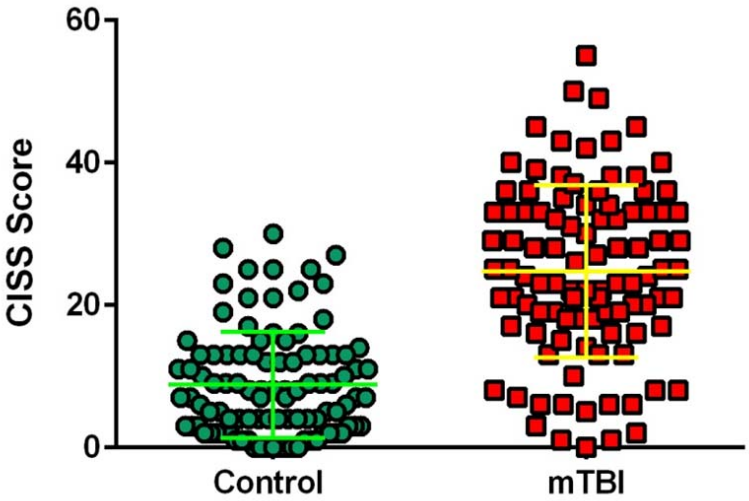
9) mTBI group had a significantly reduced NPC compared to the control group (P < 0.0001), see figure below.



10) The KD test is used to evaluate saccadic eye movement. The KD test is based on measurement of the speed of rapid number naming and involves reading aloud a series of single-digit numbers from left to right on three test cards. KD test showed significantly longer performance time for mTBI group compared to the control group ($P < 0.0001$). The expected mean time (sec) for the KD test are: pass <45; borderline 45-60; fail >60.



11) The CISS documents the frequency of visual symptoms. Each symptom question had five possible answers with an associated value, where 4 = always, 3 = frequently, 2 = sometimes, 1 = rarely, and 0 = never. Thus, the cumulative symptoms score can vary from 0 to 60. An average normal adult should score <21 points. There was a significantly higher score on CISS score for the mTBI group ($P < 0.001$), see figure below.



Subtask 3: Complete final report: NO INITIATED (A 6-month No Cost Extension was approved to complete data analysis and manuscript writing.)

KEY RESEARCH ACCOMPLISHMENTS:

- Received Yr-2 continuing review approval by WAMC IRB
- Received Yr-2 continuing review approval by USAMRMC HRPO
- Collected Data in 100 mTBI subjects
- Collected Data in 100 age-matched control subjects

REPORTABLE OUTCOMES:

- Presented lecture at WAMC Annual Research Symposium on 4 May 2016. First Place prize for faculty lectures. (Appendix A).
- Presented poster at the American Optometric Association (AOA) Meeting on 2 July 2016 Selected on Top 5 research presentation at the meeting (Appendix B).
- Presented lecture at the American Optometric Association (AOA) Meeting on 3 July 2016 (Appendix C).
- Presented poster at the Military Health System Research Symposium (MHSRS) on 16 August 2016. Second Place prize for all posters in the category (Appendix D)
- Published Article: Walsh, D.V., Capo-Aponte, J.E., Beltran, T.A., Cole, W.R., Ballard, A.D., Dumayas, J.Y. Assessment of the King-Devick (KD) test for screening acute mTBI/concussion in warfighters. Journal of the Neurological Sciences. 2016. 370: 305-9. (Appendix E)

CONCLUSION:

Preliminary results showed that three of the eight PLR parameters are statistically different between the groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. In addition, the KD test, NPC rule, and the CISS survey showed sensitivity in identifying military personnel with mTBI.

REFERENCES:

- Defence and Veterans Brain Injury Center (DVBIC), DoD Worldwide Numbers for TBI. 2015. http://www.dvbic.org/dod-worldwide-numbers-tbi.
- Marion, D.W., et al., Proceedings of the military mTBI Diagnostics Workshop, St. Pete Beach, August 2010. J Neurotrauma, 2011. 28(4): p. 517-26.
- Capó-Aponte, J.E., et al. 2013. Pupillometry as an objective biomarker for the diagnosis of blast-induced mild traumatic brain injury. Journal of Spine. Supplement Brain & Spinal Cord Injury. 2: S4-004: 1-5.

APPENDICES:

- Appendix A: Lecture at WAMC Annual Research Symposium (4 May 2016)
- Appendix B: Poster at American Optometric Association (2 July 2016)
- Appendix C: Lecture at American Optometric Association Meeting (3 July 2016)
- Appendix D: Poster at Military Health System Research Symposium (16 Aug 2016)
- Appendix E: Article published in the Journal of the Neurological Sciences: Assessment of the King-Devick (KD) test for screening acute mTBI/concussion in warfighters (Sep 2016)

Pupillometry and Saccades as Objective mTBI Biomarker

RIF13R623
W81XWH-14-C-0048

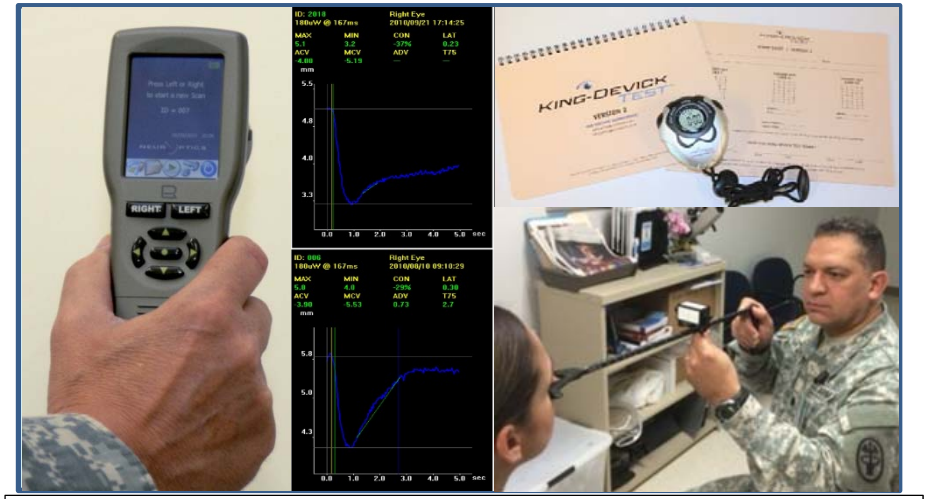
PI: LTC Jose Capo-Aponte, OD, PhD **Org:** Womack Army Medical Center/Geneva Foundation **Award Amount:** $491,815

Study/Product Aim(s)

- The DOD reported 333,169 cases of traumatic brain injury (TBI) confirmed since 2000, with 82.4% diagnosed with mild TBI (mTBI)
- mTBI diagnosis is challenging for the military due to lack of objective assessment tools
- The aim of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for identification of Warfighters with acute mTBI using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively.

Approach

100 acute mTBI (≤72 hrs post injury) and 100 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center. The study will determine within each group the effectiveness of these COTS tests, individually and/or in combination, to correctly identify patients with mTBI.



Accomplishment: Preliminary results showed 3 of 8 PLR parameters are statistically different between groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. KD test and NPC are also significantly effected in mTBI group.

Timeline and Cost

Activities FY	15	16	17
Task 1: Administrative Requirements			
Task 2: Data Collection on Military Personnel at WAMC			
Task 3: Data Analysis and Report Writing			
Estimated Budget ($K)	**$255.9**	**$235.9**	**NTE**

Updated: (24 Oct 2016)

Goals/Milestones

FY15 Goals – Study initiation / Initiate Data collection

- ☑ Hire study staff and purchase equipment/supplies
- ☑ Initial protocol approval by WAMC IRB and MRMC HRPO
- ☑ Enroll 100 mTBI subjects
- ☑ Enroll 100 age-matched non-TBI subjects

FY16 Goals – Cont. Data collection / Data Analysis / Reports

- ☑ Continuing review approval by WAMC IRB and MRMC HRPO
- ☑ Cont. enrollment mTBI
- ☑ Cont. enrollment age-matched non-TBI subjects
- ☐ Data Analysis and Report Writing (in Progress)

Comments/Challenges/Issues/Concerns

- Staff hiring issues delayed study completion; however a 6-month No Cost extension was approved

Budget Expenditure to Date

Projected Expenditure: $393,452
Actual Expenditure: $287,919

APPENDIX A

Validation of Visual Objective Biomarkers for Acute non-Blast Mild Traumatic Brain Injury (mTBI)

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Department of Optometry
Womack Army Medical Center, Fort Bragg, NC

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Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

The authors have no financial interest on any of the products included in this study.

Funded by US Army Medical Research and Materiel Command (USAMRMC), FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). Award # W81XWH-14-C-0048.

UNCLASSIFIED 2

Introduction

- The DOD reported that over 340,000 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.5%.
- The diagnosis of mTBI has been a challenge for the military primarily because:
  - Lack of objective assessment tools
  - Diagnosis is based on self-reported symptoms by injured Warfighters
  - Overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder
- Prompt and accurate diagnosis and management of mTBI generally increases prognosis for recovery and safe return to duty (RTD).
- Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma.

UNCLASSIFIED 3

Introduction

Gaps

- Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to diagnose Warfighters with mTBI/concussion.
- Valid objective markers are important in the field to assist deployed clinicians to make an accurate determination of fit-for-duty (FFD)/RTD or evacuation.
- DoD WG- Ideal tool must be: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, and low cost.

Objectives

- This study investigates oculomotor functions as potential biomarkers for acute mTBI: pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements
- Approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision
- It is not surprise that the patient with TBI may manifest visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.

UNCLASSIFIED 4

Methods: Design

- Case-Control Correlational
- 200 AD military personnel
  - 100 acute mTBI: 87 males & 13 females
    - Documented mTBI/concussion during the acute phase (≤ 72 hrs)
      - ≤ 30 min Loss of Consciousness
      - ≤ 24 hrs Post-Traumatic Amnesia
      - ≤ 24 hrs Alteration of Mental State
      - Glasgow Coma Scale score (13 – 15)
      - Normal structural brain imaging
  - 80 age-matched Non-TBI; 79 males & 21 females
- Age ranged from 19 to 44 years; Mean age 26.31±5.81 years

UNCLASSIFIED 5

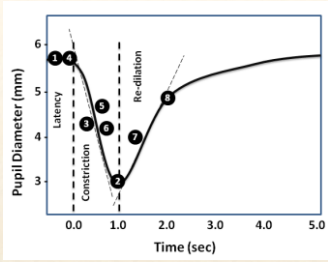
Methods: Pupillometry

NeurOptics PLR-200
Hand-held, easy to use, quick, deployable, objective, non-invasive, requires no specialized training and causes no added discomfort or risk to the patient.

- Monocular Infrared pupillometer under mesoscopic (dim) conditions (~3 cd/m²).
- Subject fixated with the non-tested eye on a distance target (10 ft).
- Stimulus: 180 µW light for 185 msec.
- 8 pupillary light reflex (PLRs) were recorded twice in the right eye and then twice in the left, alternating between eyes with an interval of about 10 seconds between recording.

UNCLASSIFIED 6

Methods: Pupillometry

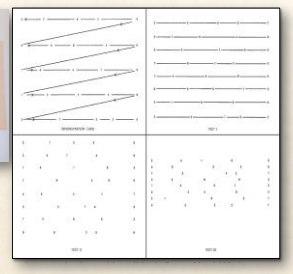


1) Max. Pupil Diameter
2) Min. Pupil Diameter
3) % of Constriction
4) Constriction Latency
5) Avg. Constriction Velocity
6) Max. Constriction Velocity
7) Avg. Dilation Velocity
8) 75% Recovery of Dilation

Methods: Near Point Convergence

- Near Point Rule was used to examine NPC
- 20/30 Snellen single letter stimulus.
- Repeated 2X

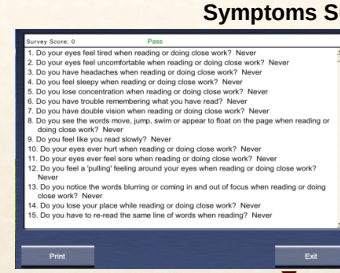
Methods: King-Devick Test



Eye movement/version test: Subject is asked to read numbers aloud while being timed. Speed and accuracy is emphasized.

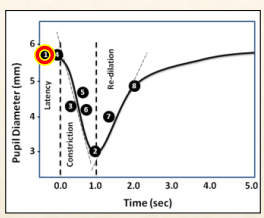
Methods: CISS

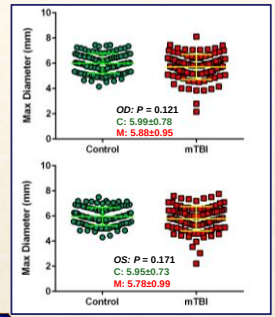
Convergence Insufficiency Symptoms Survey



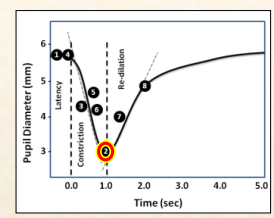
- Score based on scale:
  - always (4)
  - frequently (3)
  - sometimes (2)
  - rarely (1)
  - never (0)
- Passing score ≤20

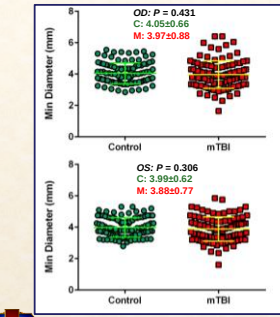
Results: Maximum Diameter



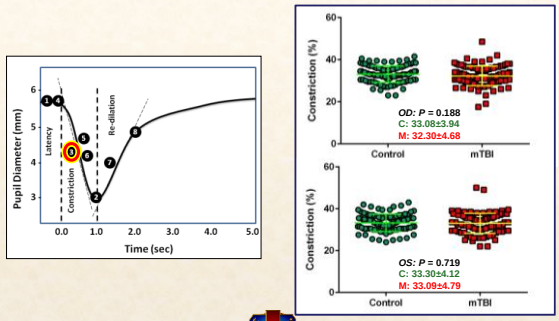


Results: Minimum Diameter

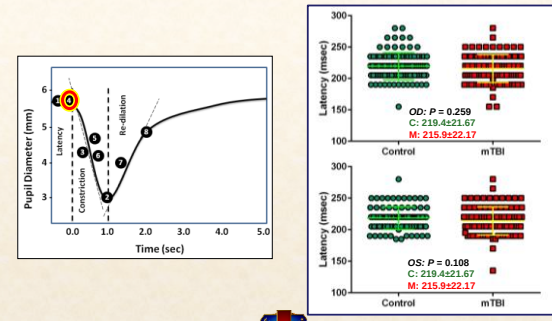




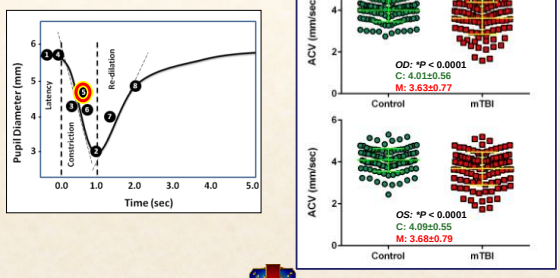
Results: % of Constriction



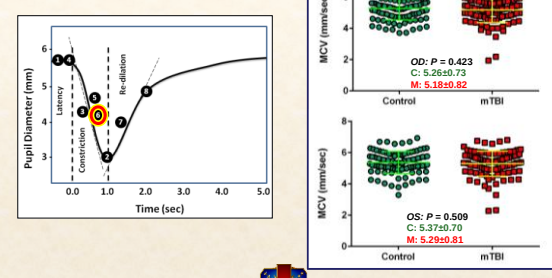
Results: Constriction Latency



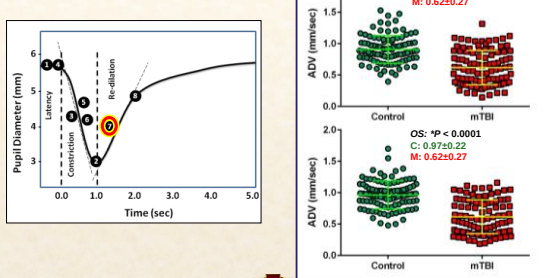
Results: Avg Constriction Velocity



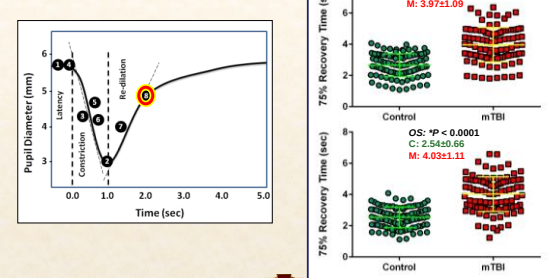
Results: Max Constriction Velocity



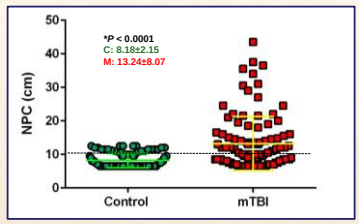
Results: Avg Dilation Velocity



Results: 75% Dilation Recovery Time



Results: Near Point of Convergence



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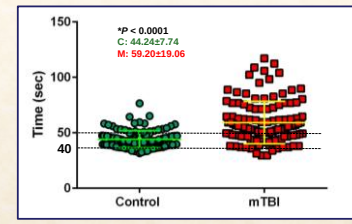
Results: King-Devick Test

(Subjective and uses baseline pre-injury time)



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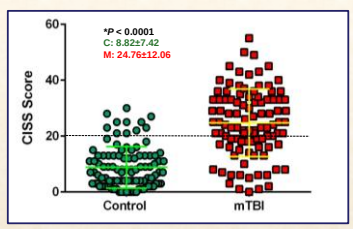
Results: CISS

(Subjective)



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Conclusion

- Oculomotor functions tests are effective tools to identify mTBI
  - Pupillometry: PLR (i.e., ACV, ADV, T75%) – Objective test
  - NPC rule: Convergence eye movement – Objective test
  - KD Test: Saccadic eye movement – Subjective test
  - CISS: visual symptoms has good correlation with affected visual functions
- Easily performed by subjects, including mTBI
- Easily administered by technicians (can delegate to medics)
- Faster (3 min) than conventional oculomotor examination (15 min)
  - Pupillometry = 30 sec; NPC = 15 sec; KD Test = 60 sec; CISS = 60 sec
- Provide tool to determine RTD (Military Ops) or Return-to-Play (Sport)
- Future Direction:
  - Develop concussion risk matrix/algorithm based on parameters sensitivity and specificity to assist in RTD/RTP decision

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Acknowledgement

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- Defense and Veterans Brain Injury Center / WAMC Department of Brain Injury Medicine
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- The Geneva Foundation / WAMC
  - Joseph Y. Dumayas
  - Dr. Ashley Ballard
- US Army Aeromedical Laboratory
  - LTC David V. Walsh

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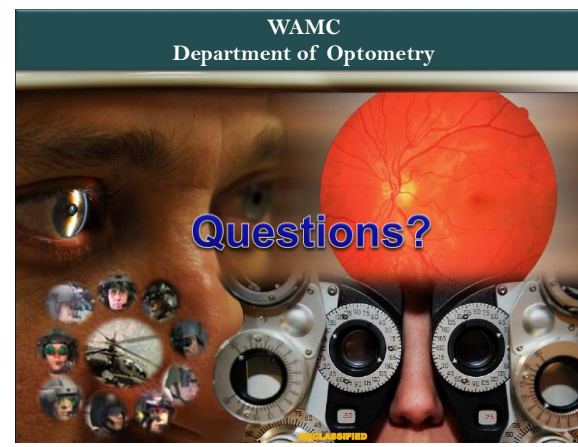

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APPENDIX B Validation Study of Visual Objective Biomarkers for Acute Mild Traumatic Brain Injury

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Thomas Beltran, BS[3] Wesley Cole, PhD[3]

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[2]U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL
[3]Department of Brain Injury Medicine WAMC; Defense and Veterans Brain Injury Center, Fort Bragg, NC

Introduction

The Department of Defense reported that over 340,000 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.5% of all cases. Unfortunately, Warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. Currently, there is a lack of mTBI objective biomarkers, and this study aims to identify and validate objective visual biomarkers for mTBI.

Methods

200 military personnel (100 acute mTBI (≤ 72 hrs) and 100 age-matched Controls; 19 to 44 yrs with mean age 26.31±5.81 yrs) were evaluated with three tests and a subjective questionnaire. Pupillary Light Reflex (PLR) functions were measured with a hand-held monocular infrared pupillometer (NeurOptics PLR-200 **(Fig 1)**. Near Point of Convergence (NPC) was measured with a NPC rule **(Fig 2)**. Saccadic eye movement function was assessed with the King-Devick (KD) Test **(Fig 3)**. The Convergence Insufficiency Symptoms Survey (CISS) was used to assess visual symptoms **(Fig 4)**.

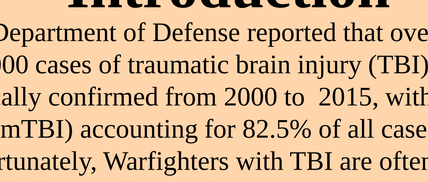

Fig 1. Left: Demonstration of pupil assessment with PLR-200 monocular pupillometer. Right: Typical PRL output curve with eight outcome measures demonstrated: 1) Max. Pupil Diameter; 2) Min. Pupil Diameter; 3) % of Constriction; 4) Constriction Latency; 5) Avg. Constriction Velocity; 6) Max. Constriction Velocity; 7) Avg. Dilation Velocity; 8) 75% Recovery of Dilation.

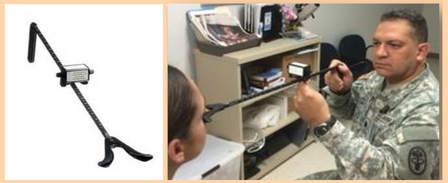

Fig 2. Left: Near Point Convergence (NPC) rule. Right, demonstration of NPC assessment using a 20/30 Snellen single letter stimulus.

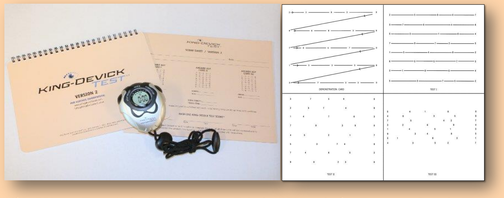

Fig 3. Left: King-Devick (KD) Test. Right: Top left, Demo Card; Top right Test 1; Lower left, Test 2; Lower right, Test 3. Cumulative times were recorded.

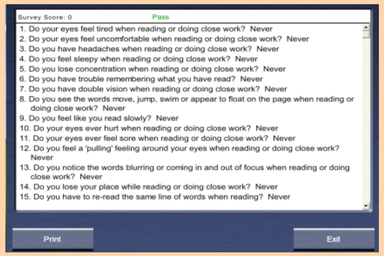

Fig 4. Convergence Insufficiency Symptoms Survey (CISS). Each question was scored based on severity: always (4), frequently (3), sometimes (2), rarely (1), and never (0). A passing score is ≤ 21.

Results

Of the 8 PLR outcome measures, only average the constriction velocity, average dilation velocity and 75% recovery time were significantly affected in mTBI group **(Figs 5, 6 and 7)**. In addition, mTBI group had significantly higher scores for NPC (receded NPC; $P < 0.0001$), KD Test (took longer; $P < 0.0001$), and CISS (more symptoms; $P < 0.0001$) than Controls as shown in **Figs 8, 9, and 10**.

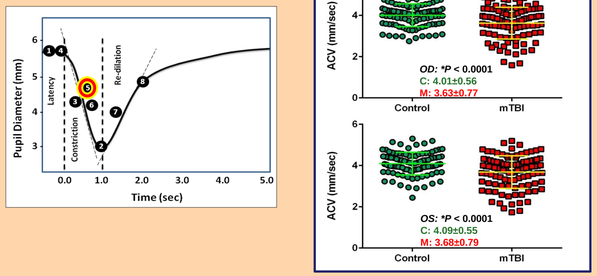

Fig 5. Average Constriction Velocity. mTBI group showed slower average constriction velocity than Control group.

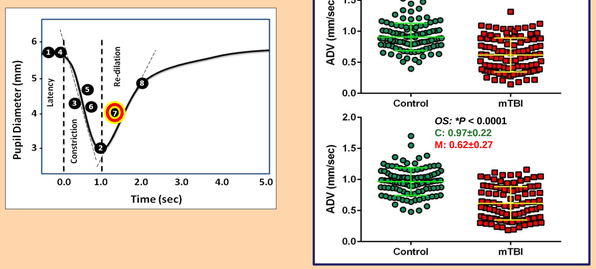

Fig 6. Average Dilation Velocity. mTBI group showed slower average dilation velocity than Control group.

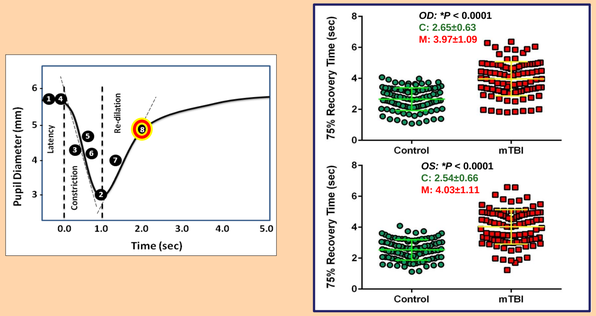

Fig 7. 75% Recovery (re-dilation) Time. mTBI group showed longer time to reach 75% re-dilation than Control group.

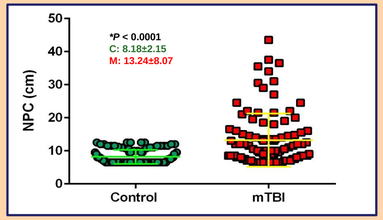

Fig 8. NPC. mTBI group had more receded NPC than Controls.

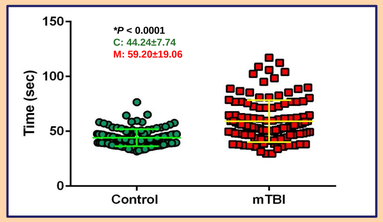

Fig 9. KD test. mTBI group took longer to complete than Controls.

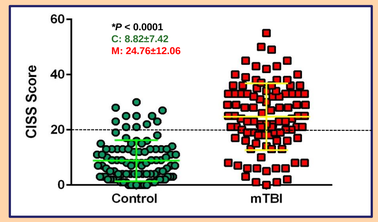

Fig 10. CISS. mTBI group showed more symptoms (higher scores) than Controls.

Conclusion

Results strongly suggest the PLR (i.e., ACV, ADV, T75%) and NPC tests can serve as objective biomarkers for mTBI. The CISS and KD tests also appear to be useful for identifying mTBI, despite of being subjective. These tests that can be quickly administered by non-eye care providers and easily interpreted by frontline providers, which is vitally important due to the increased risk of sending an injured Warfighter back to the fight and exposing him or her to greater damage to an already injured brain.

Disclaimer: The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.
Funding: US Army Medical Research and Materiel Command, FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs , Award # W81XWH-14-C-0048.

APPENDIX C

Validation Study of Visual Objectives Biomarkers for Acute Mild Traumatic Brain Injury

American Optometric Association Meeting
3 July 2016

LTC Jose E. Capó-Aponte, OD, PhD, FAAO

Department of Optometry
Womack Army Medical Center, Fort Bragg, NC

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Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

The authors have no financial interest on any of the products included in this study.

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UNCLASSIFIED 2

Introduction

- The DOD reported that over 340,000 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.5%.
- The diagnosis of mTBI has been a challenge for the military primarily because: lack of objective assessment tools; overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD); interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters.
- Prompt and accurate diagnosis and management of mTBI generally increases an individual's prognosis for neurological recovery and safe return to duty (RTD).
- Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma.
- Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.

UNCLASSIFIED 3

Introduction

Gaps

- Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.
- Ideal tool must be: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, and low cost.
- Valid objective markers are particularly important in the field to assist deployed clinicians to make an accurate determination of fit-for-duty (FFD)/RTD or evacuation.

Objectives

- Since approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision, it is not unexpected that the patient with TBI may manifest a host of visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.
- This study investigates pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements as potential biomarkers for acute mTBI.
- The study included 3 eye procedures and 1 visual symptoms questionnaire
- 10 min test battery.

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Methods: Design

- Case-Control Correlational
- 200 AD military personnel
  - Age ranged from 19 to 44 years; Mean age 26.31±5.81 years
    - 100 acute mTBI: 87 males & 13 females
      - Medically documented mTBI/concussion during the acute phase (≤ 72 hrs)
        - » ≤ 30 min Loss of Consciousness
        - » ≤ 24 hrs Post-Traumatic Amnesia
        - » ≤ 24 hrs Alteration of Mental State
        - » Glasgow Coma Scale score (13 – 15)
        - » Normal structural brain imaging
    - 100 age-matched Non-TBI; 79 males & 21 females

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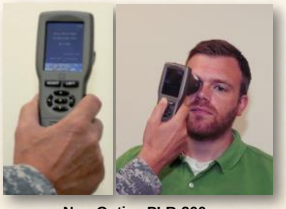
Methods: Pupillometry



NeurOptics PLR-200
Hand-held, easy to use, quick, deployable, objective, non-invasive, requires no specialized training and causes no added discomfort or risk to the patient.

- Monocular Infrared pupillometer under mesoscopic (dim) conditions (~3 cd/m²).
- Subject fixated with the non-tested eye on a distance target (10 ft).
- Stimulus: 180 µW light for 185 msec.
- 8 pupillary light reflex (PLRs) were recorded twice in the right eye and then twice in the left, alternationg between eyes with an interval of about 10 seconds between recording.

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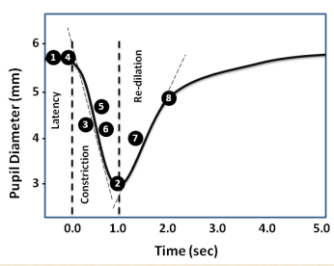
Methods: Pupillometry

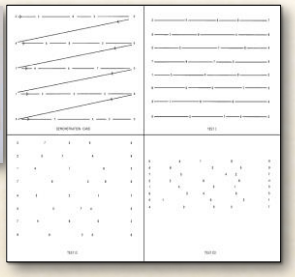


1) Max. Pupil Diameter
2) Min. Pupil Diameter
3) % of Constriction
4) Constriction Latency
5) Avg. Constriction Velocity
6) Max. Constriction Velocity
7) Avg. Dilation Velocity
8) 75% Recovery of Dilation

Methods: Near Point Convergence

- Near Point Rule was used to examine NPC
- 20/30 Snellen single letter stimulus.
- Repeated 2X

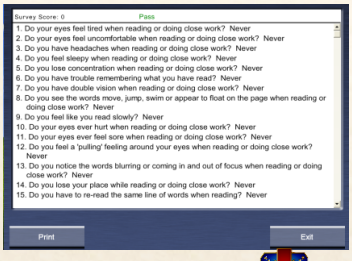
Methods: King-Devick Test



Eye movement/version test: Subject is asked to read numbers aloud while being timed. Speed and accuracy is emphasized.

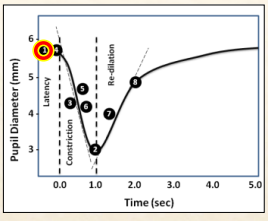
Methods: CISS

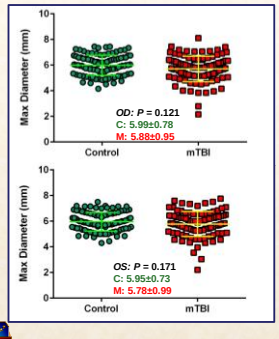
Convergence Insufficiency Symptoms Survey



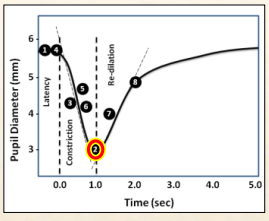
- Score based on scale:
  - always (4)
  - frequently (3)
  - sometimes (2)
  - rarely (1)
  - never (0)
- Passing score ≤20

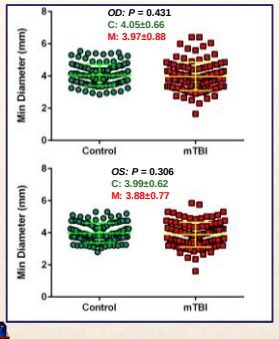
Results: Maximum Diameter



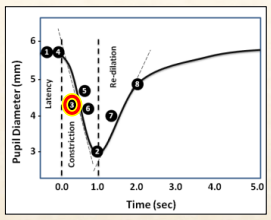


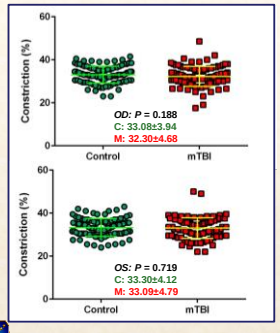
Results: Minimum Diameter





Results: % of Constriction





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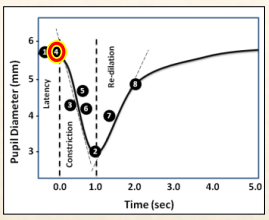
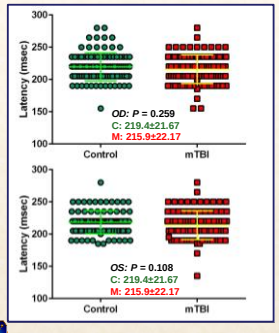
Results: Constriction Latency





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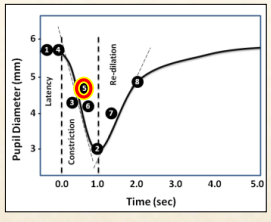
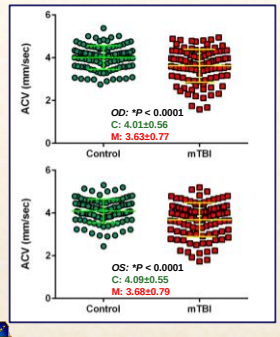
Results: Avg Constriction Velocity





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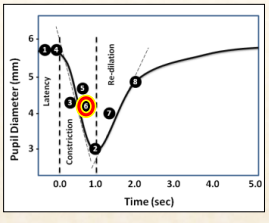
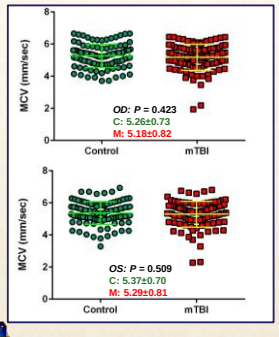
Results: Max Constriction Velocity





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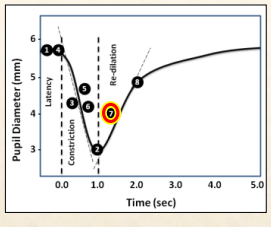
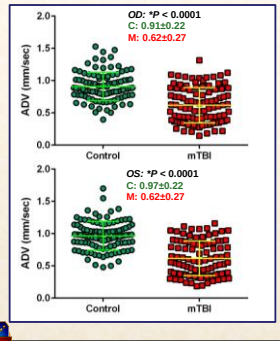
Results: Avg Dilation Velocity





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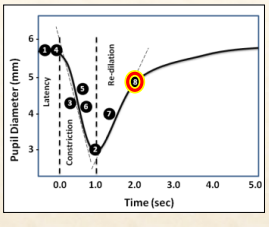
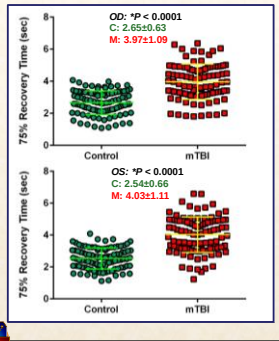
Results: 75% Dilation Recovery Time





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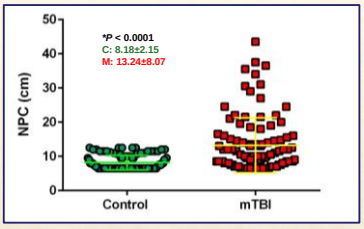
Results: Near Point of Convergence



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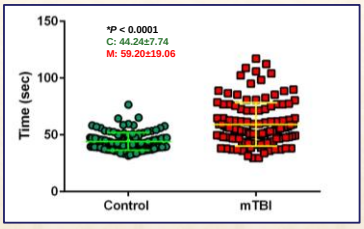
Results: King-Devick Test

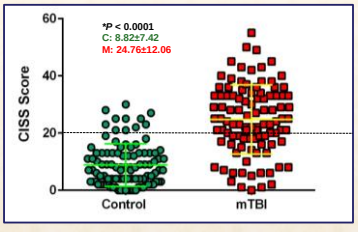
(Subjective)



UNCLASSIFIED 20

Results: CISS

(Subjective)



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Discussion

- All methods proof effective tool to differentiate mTBI Vs. Controls.
  - Objective component: PLR (i.e., ACV, ADV, T75%)
  - Objective and Subjective component: NPC
  - Subjective component: KD test
  - Good correlation with CISS
- Easily performed by subjects, including mTBI
- Easily administered by technicians
- Faster (3 min) than conventional oculomotor examination (15 min)
- Provide tool to expedite mTBI diagnosis and management
  - Delegate to technician/medics
- Future Direction
  - Develop decision matrix to assist medical personnel make RTD decision

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Acknowledgement

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  - Thomas A. Beltran
- Defense and Veterans Brain Injury Center / WAMC
  - Dr. Wesley R. Cole
- The Geneva Foundation / WAMC
  - Joseph Y. Dumayas
  - Dr. Ashley Ballard
- US Army Aeromedical Laboratory
  - LTC David V. Walsh

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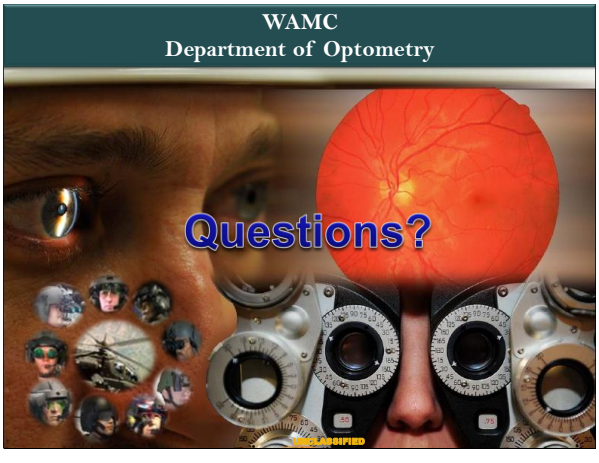

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APPENDIX D Validation of Visual Objective Biomarkers for Acute Concussion

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[1]Department of Optometry, WAMC, Fort Bragg, NC; [2]Department of Clinical Investigations, WAMC, Fort Bragg, NC; [4]U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL; [5]Geneva Foundation[1]Intrepid Spirit, Womack Army Medical Center (WAMC), Defense and Veterans Brain Injury Center, GDIT, Fort Bragg, NC;

Introduction

According to the DoD, 82.5% of the 340,000 diagnosed traumatic brain injuries (TBI) since 2000 have been concussion/ mild TBI (mTBI). Accurate and quick diagnosis of mTBI can assist with return to duty (RTD) decisions. However, there is a lack of objective mTBI biomarkers. As approx. 30 areas of the brain and 7 of 12 cranial nerves deal with vision, it is reasonable to expect visual problems post mTBI. This study aims to identify and validate objective visual biomarkers for mTBI.

Methods

200 military personnel (100 acute mTBI (≤ 72 hrs) and 100 age-matched Controls; 19 to 44 yrs with mean age 26.31±5.81 yrs) were evaluated with three tests and a self-report questionnaire. Pupillary Light Reflex (PLR) functions were measured with a hand-held monocular infrared pupillometer (NeurOptics PLR-200; **Fig 1)**. Near Point of Convergence (NPC) was measured with a NPC rule **(Fig 2)**. Saccadic eye movement function was assessed with the King-Devick (KD) Test **(Fig 3)**. Visual symptoms were assessed with the Convergence Insufficiency Symptoms Survey (CISS) **(Fig 4)**.

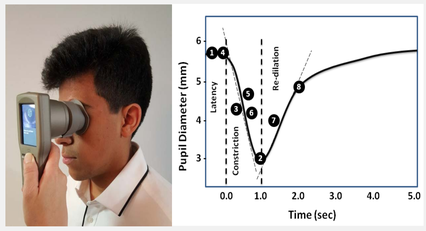


Fig 1. Left: Demonstration of pupil assessment with PLR-200 monocular pupillometer. Right: Typical PRL output curve with eight outcome measures demonstrated: 1) Max. Pupil Diameter; 2) Min. Pupil Diameter; 3) % of Constriction; 4) Constriction Latency; 5) Avg. Constriction Velocity; 6) Max. Constriction Velocity; 7) Avg. Dilation Velocity; 8) 75% Recovery of Dilation.

Fig 2. Left: Near Point Convergence (NPC) rule. Right, demonstration of NPC assessment using a 20/30 Snellen single letter stimulus.

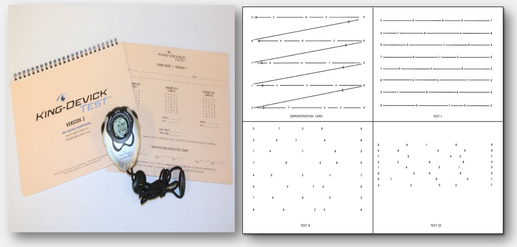


Fig 3. Left: King-Devick (KD) Test. Right: Top left, Demo Card; Top right Test 1; Lower left, Test 2; Lower right, Test 3. Cumulative times were recorded.

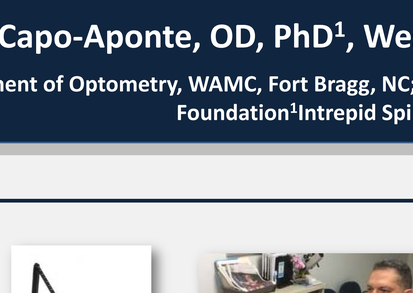
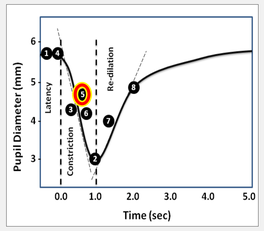


Fig 4. Convergence Insufficiency Symptoms Survey (CISS). Each question was scored based on severity: always (4), frequently (3), sometimes (2), rarely (1), and never (0). A passing score is ≤ 21.

Results

Three of the eight PLR outcome measures were significantly impacted by group status: Average Constriction Velocity (ACV), Average Dilation Velocity (ADV), and 75% Recovery Time (T75%) (**Figs 5, 6 and 7)**. In addition, **mTBI** group had significantly higher scores for NPC (i.e. receded NPC; $p < 0.0001$), took longer on the KD Test ($p < 0.0001$), and rated more symptoms on the CISS ($p < 0.0001$) than **Controls** (**Figs 8, 9, and 10)**. Effect sizes (Cohen's *d*) were generally very large.

C: 4.01±0.56
M: 3.63±0.77
$p < 0.0001$
$d = 0.564$



C: 2.54±0.66
M: 4.03±1.11
$p < 0.0001$
$d = 1.632$

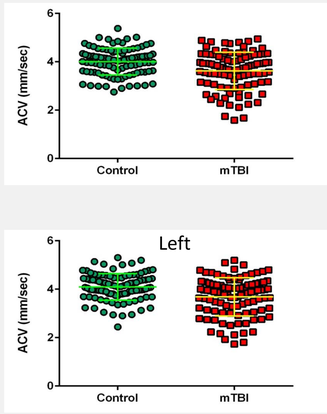
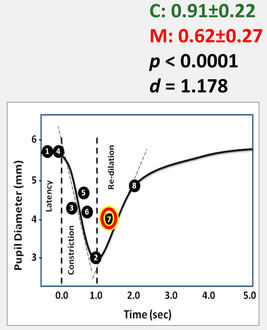


Fig 5. Average Constriction Velocity. The mTBI group showed slower right-sided average constriction velocity than the Control group.

C: 0.91±0.22
M: 0.62±0.27
$p < 0.0001$
$d = 1.178$



C: 0.97±0.22
M: 0.62±0.27
$p < 0.0001$
$d = 1.421$

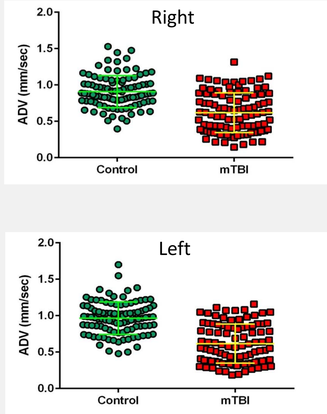
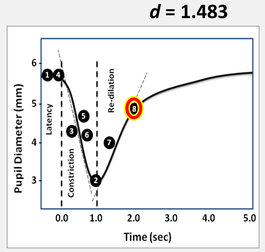


Fig 6. Average Dilation Velocity. The mTBI group showed slower average dilation velocity than the Control group.

C: 2.65±0.63
M: 3.97±1.09
$p < 0.0001$
$d = 1.483$



C: 2.54±0.66
M: 4.03±1.11
$p < 0.0001$
$d = 1.632$

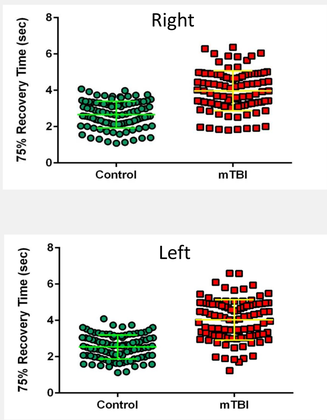


Fig 7. 75% Recovery (re-dilation) Time. The mTBI group showed longer time to reach 75% re-dilation than the Control group.

C: 8.18±2.15
M: 13.24±8.07
$p < 0.0001$
$d = 0.857$

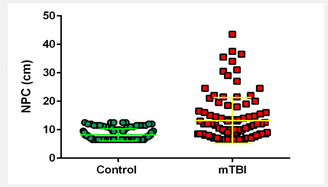


Fig 8. Near Point Convergence. mTBI group had more receded NPC than Controls.

C: 44.24±7.74
M: 59.20±19.06
$p < 0.0001$
$d = 1.028$

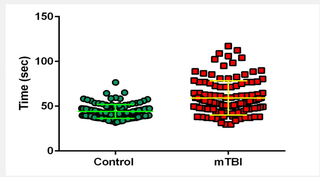


Fig 9. King-Devick Test. mTBI group took longer to complete than Controls.

C: 8.82±7.42
M: 24.76±12.06
$p < 0.0001$
$d = 1.592$

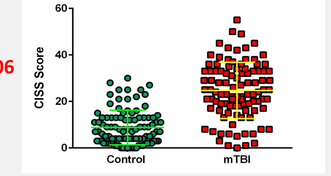


Fig 10. CISS. mTBI group showed more symptoms (higher scores) than Controls.

Conclusion

Results strongly suggest the PLR (i.e., ACV, ADV, T75%) and NPC tests could serve as objective biomarkers for acute mTBI. The CISS and KD tests also appear to be useful for identifying mTBI related problems, despite being more subjective. All of these assessments are deployable, can be quickly administered by non-eye care providers, and are easily interpreted by frontline providers. These factors are important due to the risks associated with prematurely returning an injured Warfighter to duty. Future studies should establish diagnostic algorithms.

Disclaimer: The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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APPENDIX E

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journal homepage: www.elsevier.com/locate/jns

Assessment of the King-Devick® (KD) test for screening acute mTBI/concussion in warfighters

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Military

ABSTRACT

Objectives: The Department of Defense reported that 344,030 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.3% of all cases. Unfortunately, warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. This study aims to identify and validate an eye-movement visual test for screening acute mTBI.
Methods: Two-hundred active duty military personnel were recruited to perform the King-Devick® (KD) test. Subjects were equally divided into two groups: those with diagnosed acute mTBI (≤72 h) and age-matched controls. The KD test was administered twice for test-retest reliability, and the outcome measure was total cumulative time to complete each test.
Results: The mTBI group had approximately 36% mean slower performance time with significant differences between the groups ($p < 0.001$) in both tests. There were significant differences between the two KD test administrations in each group, however, a strong correlation was observed between each test administration.
Conclusions: Significant differences in KD test performance were seen between the acute mTBI and control groups. The results suggest the KD test can be utilized for screening acute mTBI. A validated and rapidly administered mTBI screening test with results that are easily interpreted by providers is essential in making return-to-duty decisions in the injured warfighter.

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1. Introduction

The Department of Defense reported that 344,030 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.3% of all cases [1]. Warfighters who experienced mild head impacts producing subtler injuries are harder to diagnose versus those warfighters who have suffered moderate to severe head injuries. Some of the confounders in identifying post-concussive problems include the overlap of symptoms in co-morbid disorders such as post-traumatic stress disorder (PTSD) [8,20], and the difficulty in diagnosing self-reported symptoms to the health provider [19].

A recently convened military mTBI diagnostics workshop emphasized the lack of biomarkers or diagnostic tests for mTBI [15,19]. Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to diagnose warfighters with mTBI/concussion [15]. In combat or training scenarios, warfighters having cognitive and neurosensory difficulties triggered by an mTBI event can put lives and safety in danger when operating in environments that depend on optimal situational awareness and perception of the surrounding environment. Having a rapid and accurate diagnostic tool in the management and treatment of mTBI generally improves an individual's prognosis for neurological recovery [10,17,18] and safe return-to-duty (RTD) [9,11,25]. Valid diagnostic tests are particularly important in theater to assist deployed clinicians in making accurate determination of RTD or evacuation from theater. Returning a warfighter with a possible head injury back to duty prior to recovery puts the warfighter at a greater risk of disability if they suffer further brain trauma [22].

Seven of the twelve cranial nerves, along with approximately 30% of the brain [23,24], are involved in visual processing; therefore, it should be no surprise that oculomotor/saccadic eye movements are commonly affected in individuals with mTBI/concussion [2–4,7]. Saccades are rapid movements of the eyes as they shift fixation from one point to another. The King-Devick® (KD) test is a rapid, easy-to-administer eye movement test developed in 1976, and used to assess dyslexia and other learning disabilities [5]. In recent studies, the KD test has been examined as a potential screening tool for assessment of concussions in sports such as boxing, football, hockey, soccer, and rugby [5,6,12,13]. All of

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these studies have demonstrated promising results in assessing pre- and post-concussive differences which suggests the KD test could potentially be used to identify warfighters who have suffered mTBI/concussion. Finally, test–retest reliability for the KD test has been examined in previous studies and shown to be high, with intraclass correlations of 0.97 (95% confidence interval [CI] 0.90, 1.0) between measurements in the absence of concussion [5,6].

The purpose of this study was to assess an "off-the-shelf" eye movement test, the King-Devick®, in those who have experienced an acute mTBI/concussion. The results of this study may validate the use of an easy-to-administer and interpret eye movement test as a post-mTBI screening tool which can be added to a range of concussion assessment tools in assisting health-care providers with RTD decisions in warfighters.

2. Methods

2.1. Subjects

Two-hundred active duty military personnel were recruited for the study. The subjects were divided into two groups: those with diagnosed acute mTBI (≤72 h; $n = 100$) and age-matched controls ($n = 100$). The diagnosis of mTBI was made by primary care providers at a military Concussion Care Clinic based on a Glasgow Coma Scale score from 13 to 15, normal structural brain imaging, if available, and meeting at least one of the following criteria: any alteration of mental state; loss of consciousness though not exceeding 30 min; posttraumatic amnesia of no more than 24 h. Inclusion criteria for the control group were any active-duty service member with no history of mTBI/concussion. The study was approved by the Womack Army Medical Center Institutional Review Board and the US Army Medical Research and Materiel Command (USAMRMC), Human Research Protection Office. Each subject was provided written informed consent before participating in the study.

2.2. Equipment & procedures

The KD test used to evaluate saccadic eye-movement performance is shown in Fig. 1. The KD test is based on the measurement of the speed of rapid number naming and involves reading aloud a series of single-digit numbers from left to right on three progressively more difficult test cards. Standardized instructions provided with the instrument were used. The KD test was administered in a well-lit room at a normal reading distance (i.e., 40 cm) with the subject's best near-visual correction, if needed (e.g., glasses, contact lenses). To begin, a demonstration card was shown to the subject with explicit instructions on how to perform the test. The subject was instructed to read the numbers as fast as possible without making errors. If error(s) were made, and the subject returned to correct the error(s), then the error(s) were not counted. The subjects were instructed not to use their hands or fingers on the card to assist during the testing. Speed and accuracy were emphasized throughout the test and the cumulative times were recorded by the tester. The cumulative time was measured with a stopwatch, and the test was administered twice with an approximately 5-minute gap between each test administration.

2.3. Statistical analyses

Means and standard deviations were calculated for each group with cumulative time to complete each KD test being the outcome measure. A Shapiro-Wilk test for normality was performed on all data, and indicated the presence of non-normal distributions. Thus, in each group, a Wilcoxon Matched-Pairs Signed-Rank Test was used to confirm test-retest reliability by comparing the KD test results from time 1 to time 2. A Mann-Whitney *U* was performed to compare control vs. mTBI group

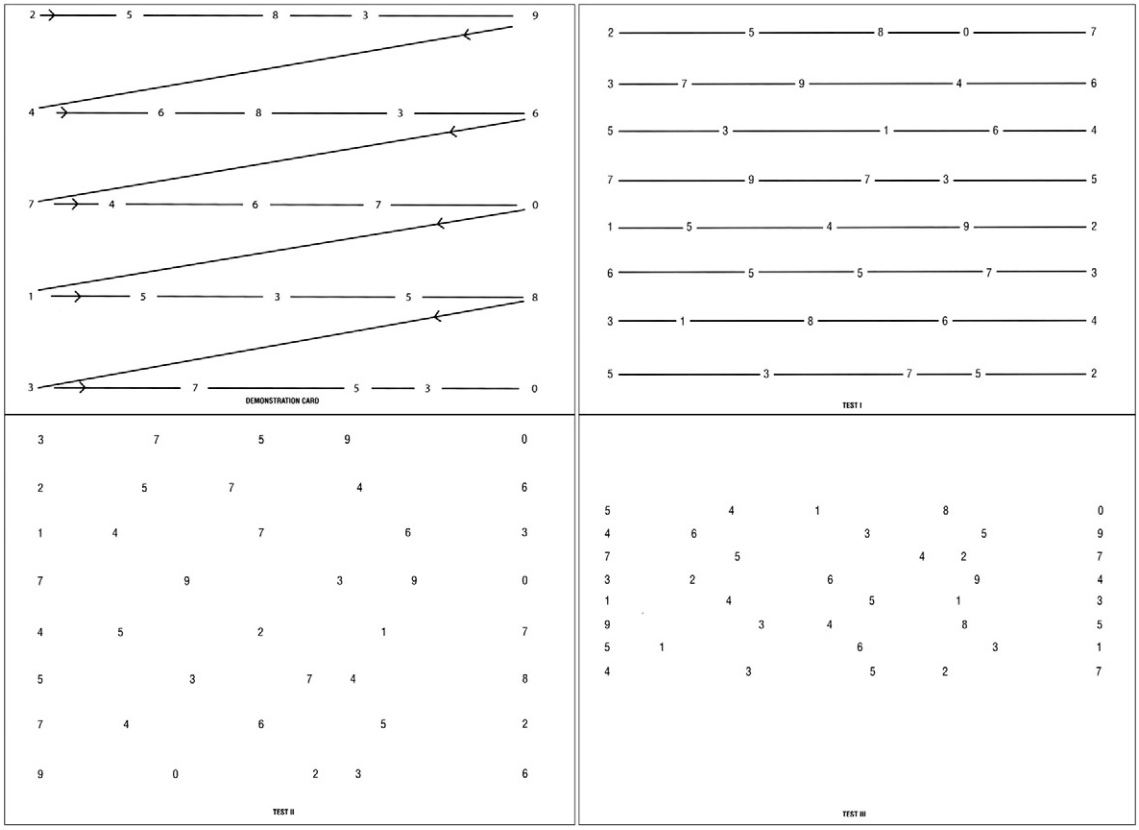

Fig. 1. King-Devick cards. The first card (top left) is the demonstration card, and subsequent cards are tests I, II, and III.

performance. Since non-parametric statistical analyses were performed on the groups' data, medians (Mdn) and Interquartile Ranges (IQR) were also reported. Statistical significance was set at $p < 0.05$, and statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 20.0 software and GraphPad Prism 6 (GraphPad Software, San Diego, CA).

3. Results

3.1. Demographics & mechanisms of injury

Demographics information of both groups is shown in Table 1. The mean age of both groups was 26.31 ± 5.83. In both groups, subjects were predominantly male (87% mTBI vs. 79% controls), Caucasian, and most were junior enlisted (E1–E4) Army soldiers. The mechanisms of injury (MOI) of the acute mTBI group are shown in Table 2. Out of the 100 mTBI subjects, a little more than two-thirds were injured due to parachute jump. Each of the remaining MOI reported (blunt force, combatives, fall, motor vehicle accident, sports/recreational activities, other) accounted for <10% of the injuries in this sample population. None of the subjects suffered from a blast-induced mTBI.

3.2. King-Devick test

Descriptive statistics are shown in Table 3. In test 1, the mean cumulative test times for the mTBI and control groups were 62.01 ± 19.91 s (95% CI [58.06, 65.96]) and 45.65 ± 8.31 s (95% CI [44.00, 47.30]), respectively. In test 2, the mean cumulative test time for the mTBI and control groups were 58.57 ± 19.71 s (95% CI [54.64, 62.47]) and 43.40 ± 8.10 s (95% CI [41.80, 45.01]), respectively. The Wilcoxon Matched-Pairs Signed-Rank Test revealed a significance difference between the two test administrations (time 1 versus time 2) in both groups (controls: $z = -5.90$, $p < 0.001$; mTBI: $z = -5.32$, $p < 0.001$). Due to the significant differences between the two tests administered to both study groups, a correlation analysis was performed. Spearman's ρ's were 0.918 ($p < 0.001$) and 0.949 ($p < 0.001$) for repeated tests for the control and mTBI groups, respectively (Fig. 2).

For test time 1, a Mann-Whitney U test revealed significant differences between the mTBI (Mdn = 58.29, IQR = 49.41–72.97 s) and control (Mdn = 44.93, IQR = 39.21–50.49 s) groups, $U = 2168$, $p \leq 0.001$ (Fig. 3). Similarly, in time 2, a significant difference was found between the mTBI (Mdn = 53.49, IQR = 45.70–70.94 s) and control (Mdn = 42.80, IQR = 37.13–47.97) groups, $U = 2380$, $p \leq 0.001$ (Fig. 3). Finally, the mTBI mean cumulative reading times were approximately 36% slower in both administration times 1 and 2.

Table 1
Demographics.

	mTBI ($n = 100$)	Controls ($n = 100$)
Age (years ± SD)	26.31 ± 5.83	26.31 ± 5.83
Sex (%)		
Males	87	79
Females	13	21
Branch		
Army	99	97
Marines	1	0
Navy	0	1
Air force	0	2
Military rank (%)		
E1–E4	62	54
E5–E6	25	17
E7–E9	3	2
CW2–CW3	2	2
O1–O5	8	25
Ethnicity (%)		
Caucasian	60	58
African-American	14	18
American-Indian	3	1
Hispanic	14	13
Asian	3	6
Other	6	4

SD = standard deviation.

Table 2
Mechanisms of injury.

	Percent (%)
Blunt force	5
Combative training	2
Fall	7
Parachute jump	69
Motor vehicle accident	6
Sports/recreational activities	5
Other	6

4. Discussion

The primary aim of the present study was to investigate the potential use of the KD test, an eye-movement screening test, as a diagnostic tool for warfighters who may have suffered an mTBI/concussion event. Results from the study demonstrated significant differences in KD test performance between the acute mTBI and age-matched control groups. The KD test showed a little more than one-third slower reading time in the mTBI group. For both groups, there was a statistically significant difference between the two test administration times, though the test-retest correlations were strong, indicating solid test-retest reliability in both the mTBI and control groups.

Numerous previous studies have validated the KD test on athletes, though with study subjects receiving baseline assessments and serving as their own controls [5,6,12,13]. Prior KD test studies utilizing separate control groups have shown significant differences between the controls and experimental groups; however, their experimental groups consisted of patients with Parkinson's disease [14] and multiple sclerosis [16], not acute mTBI as seen in the present study. But a recent KD test study on subjects recruited from an emergency department did include acute (within 72 h) mTBI patients and controls [21]. Their study did not find significant differences in KD test performance between the mTBI and control groups. This finding was contrary to previous sports-related concussions studies, and Silverberg et al. primary argument concerning the different results was their patients' mean assessment time was 31 h post-injury, whereas, the data collected in the other sports-related injury studies referenced here was within 60 min post-injury. Silverberg et al. theorized "sensitivity of the K-D may dissipate rapidly over the hours to days following an mTBI." In the present study, the subjects' mean assessment time was 2.02 days post-injury; therefore, the average post-injury was more comparable to the Silverberg et al. study. The differences in results between the studies could be due to the approximately 3.4 times greater sample size in the present study (200 vs. 59).

A limitation of the present study was no baseline KD testing was performed on the two groups of subjects. The KD test decision matrix in screening head injuries is based upon differences in baseline and post-injury KD times of the injured individuals. However, the study's significant result between the groups does strongly suggest that

Table 3
Descriptive statistics.

	mTBI		Controls	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Test 1 (s)	62.01 ± 19.91	58.29 (49.41–72.97)	45.65 ± 8.31	44.93 (39.21–50.49)
Test 2 (s)	58.57 ± 19.71	53.49 (45.70–70.94)	43.40 ± 8.10	42.80 (37.13–47.97)

s = seconds; SD = standard deviation; IQR = Interquartile Range.

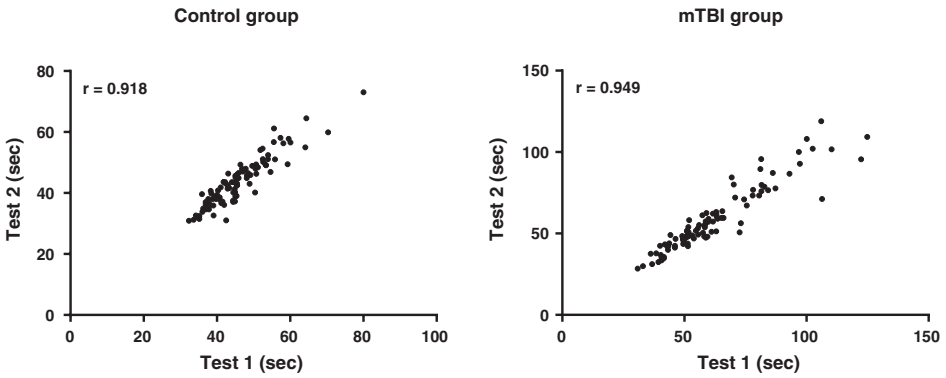

Fig. 2. Correlation graphs of KD test-retest reliability in control (left) and mTBI (right) groups. Spearman's ρ's were 0.918 ($p < 0.001$) and 0.949 ($p < 0.001$) for repeated tests for the control and mTBI groups, respectively.

baseline testing should be performed on warfighters prior to exposure to combat or training environments.

Finally, there are two drawbacks to the KD card test. First, a confounding variable with test results is the reading speed is controlled by the subject. This confounder may produce false positive or false negative results in soldiers. To reduce this issue, the KD test should not be used as a stand-alone screening test for mTBI events. Other screening tests, preferably objective, should be used in combination with the KD test when determining RTD. Second, the KD card test is that it does not provide information on what the eyes or visual system are doing while performing the test. To address this limitation, KD test technology has advanced with automated testing, and an automated KD test with eye tracking integrated is currently undergoing test-retest validity at US Army Aeromedical Research Laboratory in a separate study. However, a disadvantage of such an automated test is that it has a larger physical "footprint" (compared to KD test card), and thus may have difficulties being used as a screening device in deployment settings. The ideal screening device would be developed into smaller device such as a smartphone or tablet. With ever-advancing technology at the fingertips of front-line providers, having a quick mTBI assessment tool can not only help make rapid screening decisions, but also give eye-movement/attention information to higher echelons of care that may be helpful for any potential rehabilitation treatments on the brain-injured warfighter.

5. Conclusion

Traumatic brain injury, and especially mTBI, is an ongoing concern among the military medical community and operational commanders. Premature RTD places warfighters at greater risk of short- and long-term disability if they suffer additional concussive brain trauma. Results of the present study indicate the KD test shows promise as an additional screening tool for mTBI. However, due to intrasubject performance variability that can impact subjective test results, we recommend the KD test be utilized as a supplementary screening tool in those who have suffered an mTBI event. In addition, having pre-injury KD data will allow a more precise determination; therefore, we recommend the KD test be included as a baseline test for all warfighters prior to exposure to risk of mTBI/concussion. Having a validated, rapid, easy-to-assess mTBI brain screening test can assist frontline providers in making the RTD decision to send the warfighter back to the "fight", or to a higher echelon of care for more comprehensive tests.

Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation. I, or any of the co-authors, have no conflict of interest to report.

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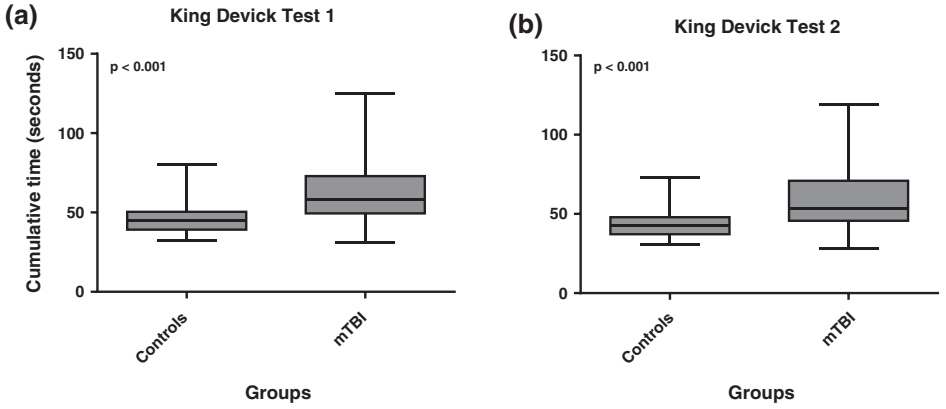

Fig. 3. Box- and-Whisker plots of (a) King-Devick test 1 controls and acute mTBI data and (b) King-Devick test 2 controls and acute mTBI data. The length of the box is the Interquartile Range (25–75%) with the middle line the median value of the data. The "whiskers" extending from the box represents the maximum and minimum range of the data. Significant differences between the controls and mTBI groups were seen in both test 1 and test 2 ($p < 0.001$).

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